Minute Cancers Arising De Novo *in the Human Large Intestine*

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In order to search for the histogenesis and progression of colorectal cancer, the background mucosas of 18 patients with a single colorectal cancer, apart from familial adenomatosis coli, were studied by a step sectioning method. Three early minute cancers (3–5 mm in diameter) were detected in the apparently normal mucosa, and two cancers in the adenoma (focal cancer in adenomatous polyp). The three early cancers had no evidence of preexisting adenoma, so they were considered to be *de novo* cancers. In form they were depressed, flat, and slightly elevated. In humans, *de novo* cancer has an important significance in histogenesis and treatment of colorectal cancer. Clinically, it is also important to recognize the early phase of colorectal cancer in flat type as well as polypoid type.

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THERE REMAINS a great controversy about the histogenesis of colorectal cancer between the adenoma–carcinoma sequence and the theory of carcinoma arising *de novo*. The adenoma–carcinoma sequence is a two-step transformation through a precursor focus of adenoma, whereas the theory of carcinoma arising *de novo* describes a direct one-step transformation of normal epithelial cells into microscopically recognizable cancerous epithelium. The adenoma–carcinoma sequence has been stressed in recent years, emphasizing the relationship between familial adenomatosis coli and colorectal cancer,[1] malignant potential of adenomas of the colon and rectum,[2] and others.

From a broad outlook on human gastrointestinal carcinogenesis, and studying many carcinomas arising *de novo* in the lower intestinal tract of the experimental animals, it must be understood that only in humans do colorectal carcinomas not necessarily evolve from adenomas. Clinically, the knowledge of whether *de novo* transformation into cancer is a main route or a rare route is important to prevent colorectal cancers. If it is a rare route, colorectal cancers can be predicted by looking for adenomas and prevented by polypectomy, but if it is a main route together with adenoma, then looking only for adenomas and polypectomy is not sufficient.

The histogenesis of colorectal cancer is both an old and a new problem. To find the early phase of colorectal cancer, we made a further study on the background mucosa of 18 new cases of single colorectal cancer in addition to the preceding report[3] by a step sectioning study.

Materials and Methods

Eighteen cases selected for this study were operated on for a colorectal cancer at the Third Department of Surgery, University of Tokyo from 1980 to 1985. All of them had a single advanced cancer at the colon and rectum, which had been diagnosed preoperatively. Eighteen patients were selected at random except that six of them were an older age group (older than 70 years), six of them were a middle-aged group, six of them were a younger aged group (younger than 39 years) (Table 1).

These patients consisted of 11 men and seven women with a total average age of 53.6 years. The sites of the cancers were the rectum in seven patients, the sigmoid colon in five patients, the descending colon in one patient, the transverse colon in three patients, the ascending colon in one patient, and the cecum in one patient. This distribution of cancers of each group was almost similar to that of clinical colorectal cancers.

The resected specimens were fixed in 10% buffered formaldehyde and standard postoperative pathologic examination was carried out. Macroscopic examination revealed adenomatous polyps in ten patients. After this examination, the entire length of the remaining tissues were longitudinally step-sectioned in 5-mm widths throughout the operative target cancers, polypoid lesions, and the apparently normal background mucosa (Fig. 1). All blocks were embedded in paraffin.

A section of 4-μm thickness was obtained from each specimen, stained with hematoxylin and eosin, and carefully examined under the microscope. An average of 51.8 sections were cut from each patient. The histopathologic findings of the operative target cancer also were

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TABLE 1. Cases of Single Advanced Cancer

	Age (yr)/sex	Target lesion (location & type)		Dukes	Length of resected bowel (mm)	Concomitant polyps
Elderly group						
Patient 1	86/F	C	Well	C	175	1
Patient 2	73/M	TCol	Well	B	290	1
Patient 3	72/M	SCol	Well	A	380	1
Patient 4	75/M	R	Mod	B	360	3
Patient 5	70/F	R	Mod	B	380	1
Patient 6	73/M	R	Well	B	260	0
Middle-aged group						
Patient 7	56/F	ACol	Mod	B	305	0
Patient 8	56/F	TCol	Well	B	220	0
Patient 9	48/F	SCol	Well	C	205	1
Patient 10	59/M	SCol	Mod	C	220	0
Patient 11	43/M	R	Well	B	305	1
Patient 12	58/M	R	Well	B	360	1
Younger group						
Patient 13	21/F	TCol	Poor	C	160	0
Patient 14	32/M	DCol	Mod	B	350	0
Patient 15	39/F	SCol	Well	B	275	0
Patient 16	27/M	SCol	Well	B	290	1
Patient 17	31/M	R	Mod	C	440	0
Patient 18	36/M	R	Poor	C	180	1

C: caecum; ACol: ascending colon; TCol: transverse colon; DCol: descending colon; SCol: sigmoid colon; R: rectum; well: well-differentiated adenocarcinoma; mod: moderately differentiated adenocarcinoma; poor: poorly differentiated adenocarcinoma.

recorded on Table 1. We studied every slide with interest in minute cancer, cancer in polyp, "microscopic adenoma,"[3] adenomatous changes of the basal cells,[4] and other pathologic findings. If necessary, adjacent serial sections were prepared to confirm the findings regarding size, character, and attendant lesions.

The findings above were mapped on each schema of the resected specimens.

Results

In total five early cancers and 22 microscopic adenomas were detected excluding 18 operative target cancers in 18 patients. Of the 5 early cancers, three were microscopically minute cancers of a flat nonpolypoid type, and two were polypoid type cancers in adenoma. The former three cancers were without any component of adenoma, so it can be concluded that they are de novo cancers. In addition to them, there were 22 microscopic adenomas and ten adenomatous polyps.

Minute De Novo *Cancer*

In total, three early cancers were detected in two patients from the older aged group. These cancers involved both extreme architecture and cytologic atypias of the colonic glandular epithelium without invading the depths of more than the muscularis mucosa. No adenomatous polyp was found in continuity with any of them.

Figures 2A and 2B are photographs of the resected specimen of Patient 2 (Fig. 2A), and its schema of step-sectioning and mapping (Fig. 2B). The specimen consisted of a 29-cm length of the large intestine which was resected by left hemicolectomy. An advanced cancer was located near the center (ulcerating type). Apart from this advanced cancer, one cancer in adenoma, two *de novo* cancers, and one microscopic adenoma were found. The *de novo* cancers were located 3.0 cm from the distal cut end (part a), and 4.0 cm from the proximal cut end (part b), and a cancer in polyp was located 7.0 cm distal from the advanced cancer. Two *de novo* cancers and one microscopic adenoma were not picked up as a "lesion" in standard macroscopic observation.

Figures 3A and 3B show a minute *de novo* cancer of Patient 2; part a. Colonic glands, which have structural and cellular atypism recognizable as adenocarcinoma, can be seen in line along the elongated fold. They are 5 mm in diameter, showing well-differentiated tubular pattern, and sharply delineated from adjacent normal epithelium. There is no evidence of accompanying adenoma. The stromal lymphocyte reaction is moderate. The height of their glands is lower than that of the adjoining normal glands, so it is a slightly depressed lesion, if the mucosas are smoothed out in the crease.

Figures 4A and 4B also show a minute *de novo* cancer (Patient 2; part b). It arises on the summit of the mucosal fold as well, and is 5 mm in diameter. It has variations in the size of the cells and nuclei, hyperchromatism, disarrangement of nuclear polarity, stratification of the cells and architectural irregularity. The cancer appears as a peduncular polyp because the elongated

fold was sectioned transversely. What appears to be a stalk is actually a nondiseased fold as confirmed by the photograph of the resected specimen and serial sectioning. If parallel sectioning to the fold is done, the height of the glands is nearly equal to that of the adjacent normal mucosa, so it is presented as a flat lesion.

Figures 5A and 5B show a minute *de novo* cancer (Patient 3). This lesion, which was clamped by a forceps at operation, is slightly higher than the adjoining normal mucosa, and was located 1.0 cm from the distal end of a 30-cm segment of the sigmoid colon and rectum. It was not picked up as a "lesion" in ordinary macroscopic observation, either. Besides this, Patient 3 had two microscopic adenomas.

Cancer in Adenoma

Two cancers in adenoma were detected in Patient 2 and Patient 5, respectively, from the older aged group. They are cancers which were observed in macroscopically detected adenomas (namely, adenomatous polyp).

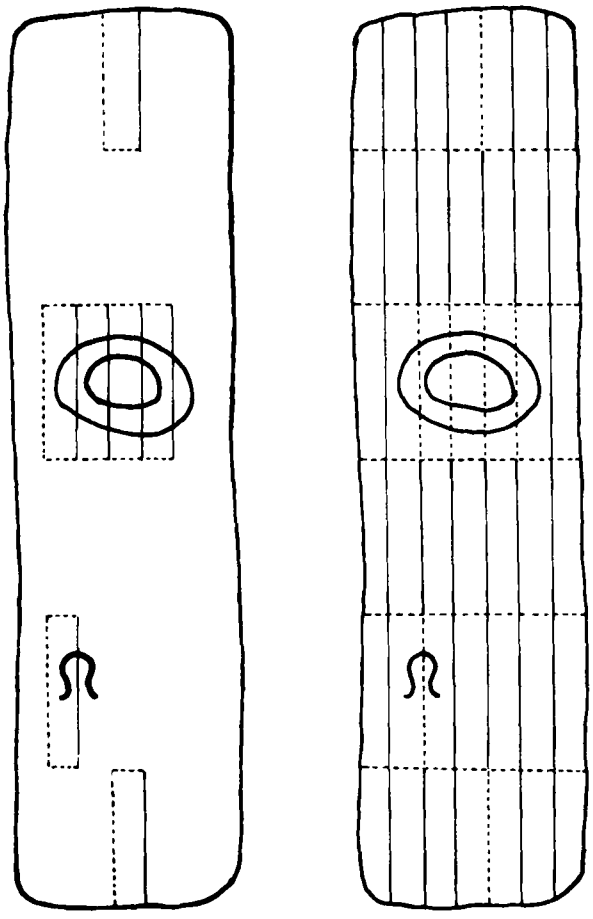
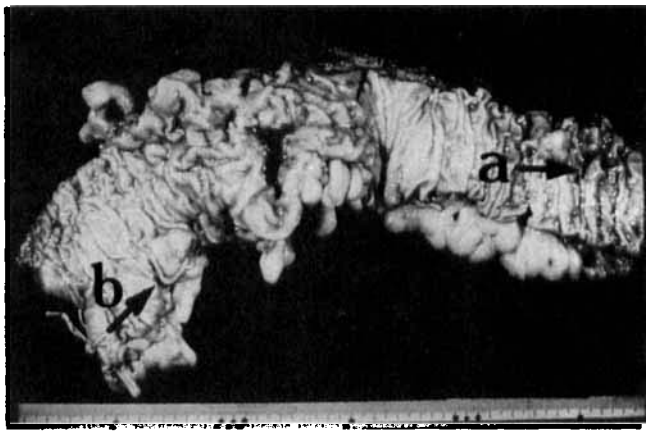
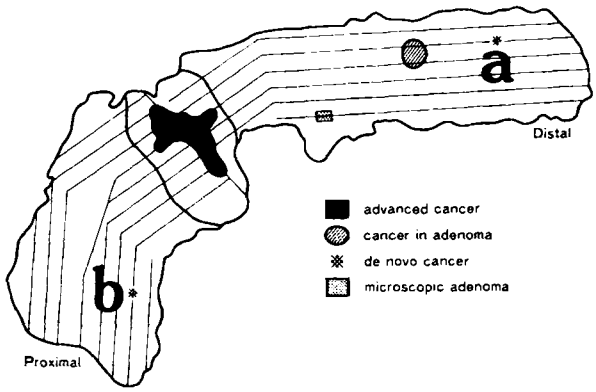


FIG. 1. After the standard postoperative pathologic examination (left), the entire length of the resected specimen is step sectioned in 5-mm widths (right).





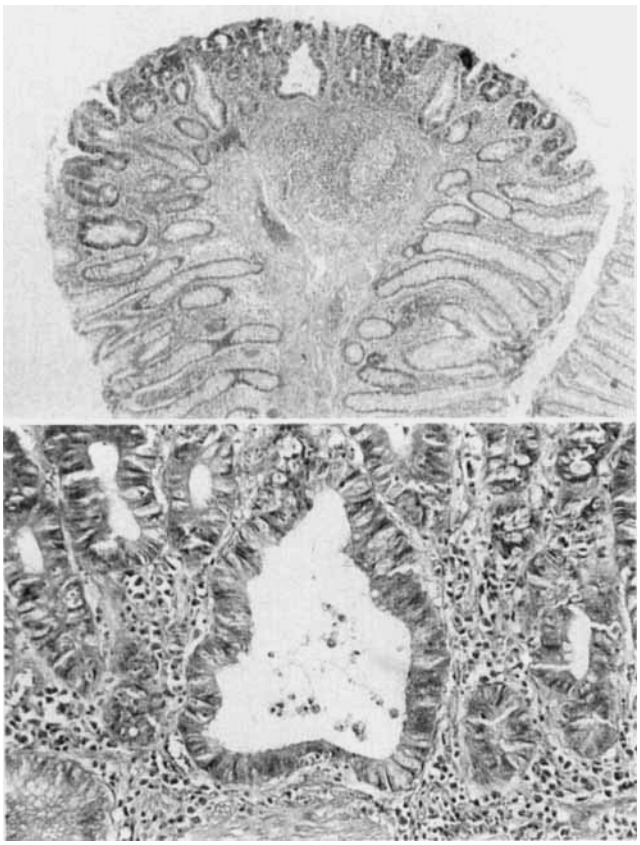
FIGS. 2A AND 2B. Photograph of the surgically resected descending colon of Patient 2 (A, top), and the schema of step sectioning and mapping (B, bottom). An advanced cancer is located near the center (ulcerating type). Two *de novo* cancers are located 3.0 cm from the distal cut end (a), and 4.0 cm from the proximal cut end (b). The former can be recognized macroscopically but only retrospectively, and the latter can not be recognized macroscopically, even retrospectively.

Microscopic Adenoma

In total, 22 microscopic adenomas were detected in the background mucosa in ten patients. Microscopic adenomas are adenomas which are so small that they can only be detected microscopically (intramucosal adenomas). Fourteen microscopic adenomas were detected in the older aged group, six in the middle-aged group, and two in the younger aged group, excluding the adenomatous polyps. Microscopic adenomas had a tendency to increase with advancing age. The majority of microscopic adenomas (21/22) displayed mild atypism. No cancer was detected in microscopic adenomas.

Discussion

In humans, the controversy as to whether the colorectal cancer arises *de novo* or whether it evolves from adenomatous polyp has continued. Except for colorectal cancer, most gastrointestinal cancers arise *de novo* in humans. In experimental animals, studies of chemically induced colonic carcinomas have shown evidence sup-



FIGS. 3A AND 3B. Minute *de novo* cancer which was found in Patient 2; a. It is on the top of the mucosal fold, and the height of their glands is lower than that of the adjacent normal glands. The growth pattern is well-differentiated tubular pattern (H & E; A, top original magnification ×40; B, bottom original magnification ×200).

porting *de novo* genesis.[5,6] It is only in colorectal cancer in humans, that the adenoma–carcinoma sequence is supposed to be the usual pathway. The reason why, colorectal cancer only in humans and not in other animals always results from adenoma, is a serious problem. Also, the reason why, differing from other gastrointestinal organs, only colorectal cancer always develops from adenoma is a question of great consequence in the field of human gastrointestinal cancer research.

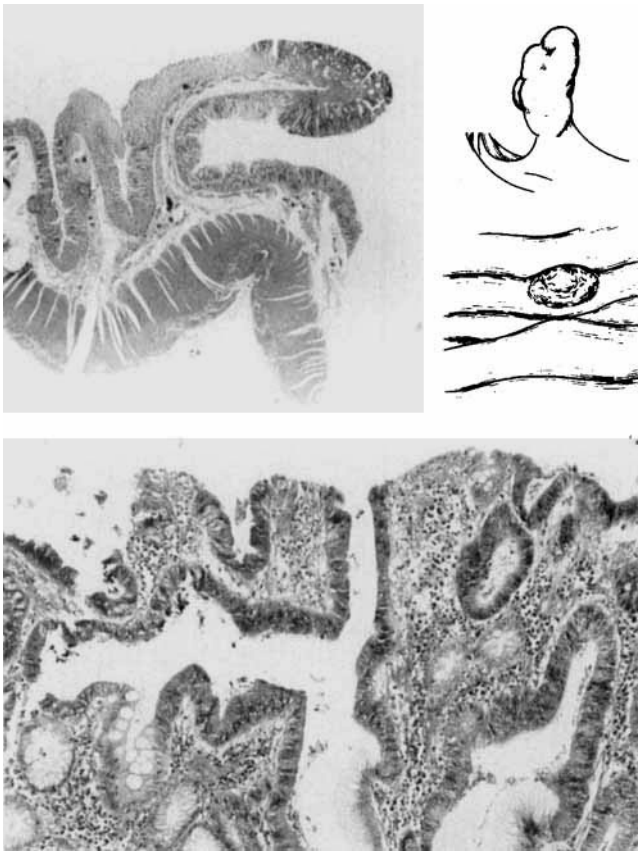
In 1959, Spratt and associates[7] examined 325 cancers of the colon, and concluded that no residuum of an adenomatous polyp was seen. After reviewing 57 polypoid lesions in 1962, Castleman and Krickstein[8] insisted similarly that the majority of cancers of the colon arise as cancer *de novo* or in villous adenomas, and not in the adenomatous polyps.

In 1959, Helwig[9] observed two small carcinomas without preexisting adenoma which arose directly from the mucosa, and ten small ones which arose in adenomas, studying 1460 necropsy specimens.

However, Morson[10] observed in 1966 that there was histologic evidence of preexisting benign tumors in 56.5% of Dukes A carcinomas. Furthermore, in 1968, he stressed that no histologic evidence of preexisting benign tumors can mean that any residual benign tumors had already been replaced by adenocarcinoma.[11] Muto *et al.*[2] asserted that no scientific evidence in support of the concept of cancer *de novo* had been described, so it remained hypothetical.

Through these arguments, the adenoma–carcinoma sequence has become predominant, because the relationship between familial adenomatosis coli and colorectal cancers, and the grossly concordance of the distributions of adenomatous polyps and of cancers in the colon constituted the theoretical basis for the adenoma–carcinoma sequence. Currently 95% to 100% of colorectal cancers are considered to arise in adenoma, except for the rare undifferentiated adenocarcinomas and carcinoma after inflammatory bowel diseases.

Referring to an alternative theory of histogenesis, the size of the cancers is often brought up. In 1962, Spratt and Ackermann[12] serially sectioned 20 small cancers of the colon, which were 2 cm or less in diameter, and

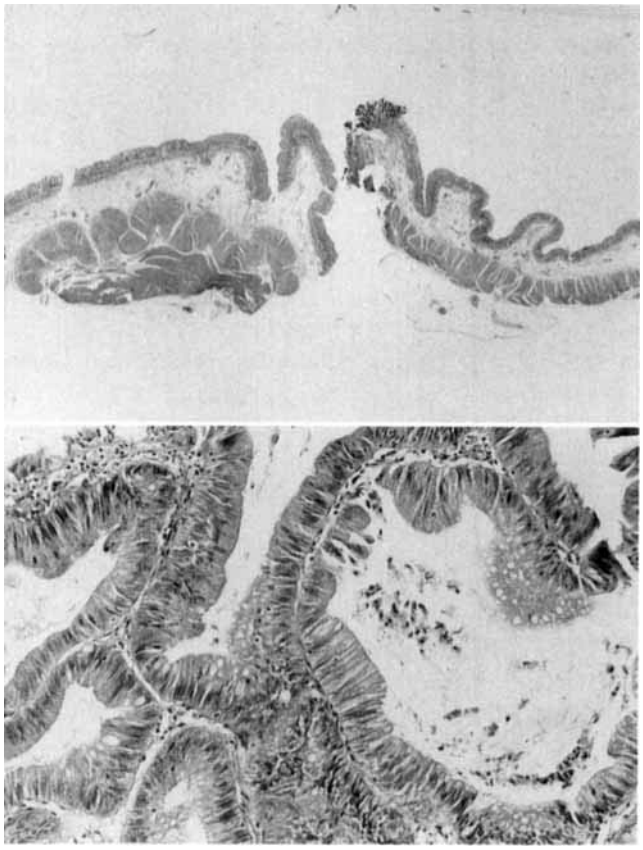


FIGS. 4A AND 4B. Another minute *de novo* cancer in Patient 2; b. (A, top) What appeared as a peduncle was confirmed to be one of the fold. *Insets:* This is not a peduncular polyp (top inset), but a flat lesion (bottom inset) (H & E, original magnification ×5). (B, bottom) Severe variation in the size of the cells and nuclei, nuclear polarity, and architectural irregularity can be seen (H & E, original magnification ×100).

found no evidence of preexisting polyps, and so persisted in believing that colorectal cancers arose *de novo*. But in 1976, Lane[13] refused it because preexisting adenomatous tissue may well have been destroyed, and whether it is found or not in the 1-cm to 2-cm size range is fairly irrelevant. To discuss *de novo* carcinoma requires a search for it in minute size range. So we used a step sectioning method throughout the entire length of the resected bowels. A step sectioning study is a useful method to search for microscopic lesions of the bowels, either in colorectal cancers[3] or in inflammatory bowel diseases.[14]

Currently our study revealed three early cancers arising *de novo*. These three minute lesions were determined as *de novo* carcinomas, for four reasons: first, residual adenoma could not be identified; second, they are small enough to deny preexisting adenomatous tissue; third, there was no connection with the primary cancer; and fourth, adenocarcinoma of the large intestine as a rule metastasizes to muscularis propria, subserosa, and serosa.

They were present in the macroscopically "normal" background mucosa. The opinion that cancer arises *de novo* has been dismissed because of the apparently normal appearance in the earliest phase. In fact, the *de novo* cancers in Patients 2 and 3 could not be found out by ordinary postoperative macroscopic screening, and only one of them was eventually detected in a retrospective examination (Patient 2; Fig. 2, part a). They were not detected by barium enema study and fiberscopic observation preoperatively. For the first time, we succeeded to detect the earliest phase of colorectal cancer by using



FIGS. 5A AND 5B. *De novo* cancer which was found in Patient 3. This lesion was clamped by a forceps at operation, but atypical glands which are slightly taller than the adjacent normal glands can be recognized as an early minute cancer without adenoma (A, top original magnification ×2; B, bottom original magnification ×200).

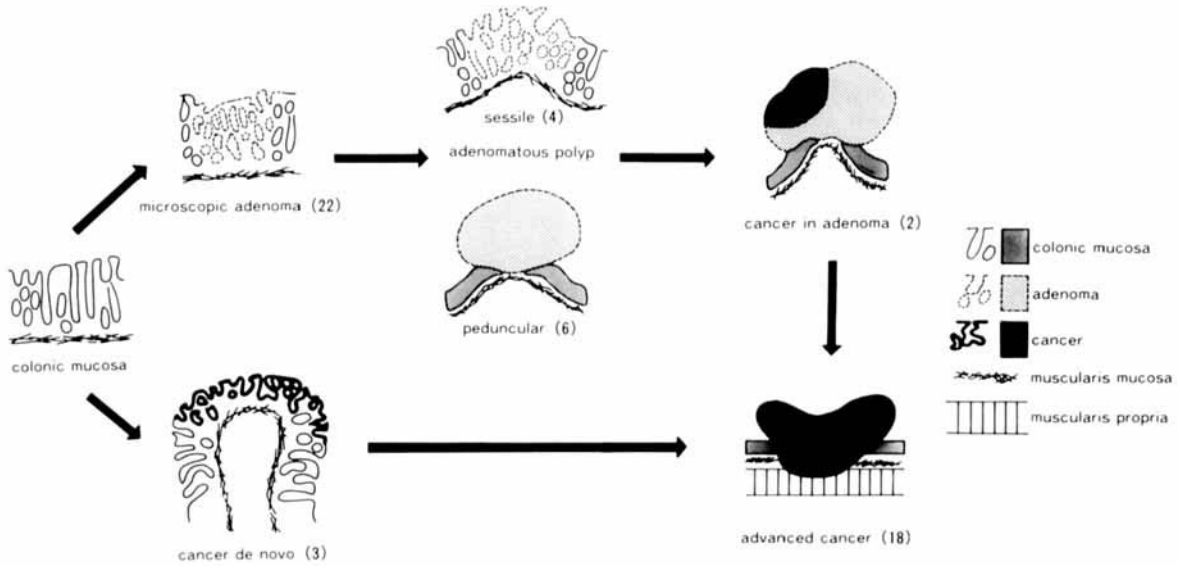


FIG. 6. Hypothetical diagram of the development of the cancers of the large intestine. Numbers in parenthesis indicate the pathologic lesions which were checked up by this study. Even in the human large bowels, cancer arising *de novo* is an important route of development as through adenoma.

a systematic step sectioning method. As far as we know, these three cancers are the earliest phase of the cancer of the large intestine.

Spjut *et al.*[15] reported five small carcinomas (3, 6, 10, 15, and 15 mm in diameter, respectively) of the large intestine. Kjeldsberg and Altshuler[16] reported two nonpolypoid carcinomas *in situ* (about 10 mm in diameter). They could be seen macroscopically, but our three minute cancers hardly can be seen macroscopically.

Figure 6 is a hypothetical diagram of the development of the colorectal cancers from normal colonic mucosa. Most of 22 microscopic adenomas are classified as mild dysplasia. And "carcinoma in adenoma" was not seen in these small flat or depressed lesions. At a very early stage, adenoma is only adenoma and it is only later that a part of adenoma develops into carcinoma by malignant transformation, probably after developing adenomatous polyps which are seen macroscopically. The development of carcinoma of the large intestine may occur either from malignancy arising *de novo* or through the pathway of an adenomatous polyp.

It is not our purpose to declare that all carcinomas of the large intestine have *de novo* origins. We just emphasize that more attention should be directed to discover small nonpolypoid lesions. The detection and removal of adenomatous polyps is of course the way of decreasing the incidence of carcinomas of the large bowels. When there are serious adenomatous polyps with focal cancer, even 10 mm or less in diameter, they have to be treated by polypectomy. But nevertheless we cannot prevent advanced cancers only by polypectomy. In light of the fact that the *de novo* development of cancer is as frequent as adenomatous development, careful endoscopic examination must be carried out to identify minute lesions which can be easily mistaken as normal mucosa. The additional use of the dissecting method[17] may increase the efficiency of this work.

Frequently, familial adenomatosis coli is stated as the best model for the study of large bowel neoplasia. But it is a peculiar model which proves that adenomatous colonic polyps become infiltrating cancers of the colon. Familial adenomatosis coli and nonfamilial adenomatosis coli have to be handled separately.

The fact that cancer in polyp changes into ulcerating type advanced cancer seldom catches our eye. And only 32 adenomas in 18 patients are too few to apply the theory of adenoma–carcinoma sequence particularly if we compare them with the numerous adenomas in familial adenomatosis coli.

Adenomas in the background mucosa have a tendency to increase with advancing age. This is a result of aging and long-continued contact with environmental agents causing adenomas,[18] as well as adenomatous changes of the basal cells.

Conclusion

The resected specimens of 18 patients without familial adenomatosis coli consisting of six in an older age group, six in a middle-aged group, and six in a young age group, who had a single advanced colorectal cancer, were entirely step-sectioned in 5 mm widths, and histopathologic observations were made.

Three minute de novo cancers were detected, and the following lesions were seen; microscopic adenomas (22), adenomatous polyps (10), and cancer in polyp (2). The microscopic adenomas had almost mild dysplasia. Even in the human large intestine without familial adenomatosis coli, cancer arising de novo is a main route of development. It is very important for pathologists and surgeons to recognize the earliest phase of colorectal cancer in the flat or depressed type as well as the polypoid type.

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